Bullet Statement Responses generated from Carchmans 4/11/94 Meeting

1. Self-administration **does not** equate with addiction potential
2. Classic addicting substances such as cocaine and heroin are have a reinforcing effect **hundreds of times higher** than nicotine or caffeine
3. When discussing effects on doparninergic reward systems, the dose of nicotine used **must** be realistic
4. Under the definition of addiction being used in these hearings, caffeine, sugar, saccharin and sex are addictive
5. Normal response to addictive drugs is to **increase** dosage all the way to **aversive or toxic levels** and beyond -- This does not happen with nicotine
6. If nicotine is addictive, why does the FDA allow nicotine patches to be used to treat the "addiction"
7. Henningfield Human Data
8. Nicotine **does not** satisfy the **"addictive craving"** of animals purposely addicted to hard drugs such as cocaine, heroin and barbiturates
9. Unlike drugs of addiction in which tolerance develops, nicotine intake by smokers **does not increase** with time
10. Abstinence from smoking **does not produce** the same changes in behavior that occurs during abstinence from drugs of addiction like cocaine and heroin
11. Smokers tend to **start** smoking high delivery cigarettes and to move to lower delivery cigarettes with time
12. **Several sensory and psychological manifestations** play important roles in the recurrence of smoking behavior
13. If nicotine is addictive, why did **Premier**, which contains nicotine, fail in the market?

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Expanded Explanations

1. Animals will self-administer a variety of compounds including caffeine, sugar, saccharin and painful stimuli besides the classical drugs of addiction such as cocaine, heroin, amphetamine and barbiturates.

2. It is very important to consider the strength of the reinforcing reaction to any particular compound. For example, animals will continue to press a lever on the order of hundreds of times in order to obtain a single dose of heroin. However, even DeNoble demonstrated that a rat will stop pressing the lever after a few level presses, if this activity is not rewarded with a dose of nicotine. In addition, the level of the dose of nicotine must be high to elicit this response, where as with heroin or cocaine, animals will work very hard to receive even small doses of the drug.

3. Experiments must be scrupulously controlled to insure that doses tested in any particular animal model are physiologically relevant to the perceived normal dose in humans. It is not meaningful to pronounce nicotine as "addictive" in humans, if it is tested in an animal at 10 to 100 times the level experienced by the smoker.

4. Animals will exhibit reinforcing behavior toward a range of substances and conditions from food, sex, sugar, saccharin, caffeine, alcohol and nitrous oxide through cocaine, heroin, amphetamine, and benzodiazipine. The relevance of the association of reinforcing behavior with addiction must be carefully weighted with the strength of that reinforcing behavior. In other words, will the animal exhibit only a little effort to continue to obtain the compound or will it go to extremes in an effort to continue to obtain the same or increasing doses of the compound.

5. Animals have been shown to continue to self-administer drugs of abuse up to and beyond levels which are considered to be aversive or toxic. In fact, for some drugs of abuse, animals will dose themselves to death. People have been shown to continue to abuse addictive substances contained in products believed to aversive to consumption (sterno, perfume, mouthwash, cough medication) or, which have been purposefully blended with compounds known to be aversive (alcohol and nicotine, sake and salt, lomotil and atropine). Smokers on the other hand do not continuely increase their dosage. Quite the contrary, it has been well demonstrated that smokers have adjusted their smoking behavior to maintain a relatively constant level of nicotine in their blood.

   The retracted DeNoble paper even indictated that the rats would stop self-administration of nicotine at a high dose level. This could be interpreted to indicate that they found the dose aversive and simply discontinued further self-adminstration.

6. The FDA classifies addictive drugs under several "Schedule Ratings" with increasing levels of severity. Decreasing schedule rating numbers make it more difficult to obtain or prescribe the drug. The FDA has not classified any of the nicotine containing "smoking abatement" devices on any schedule. Does this indicate that the FDA does not consider nicotine to be addictive?

7. Henningfield DATA

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8. Animals have demonstrated the ability to respond to and self-administer drugs which they physiologically determine to be related in effect to drugs they already self-administer. They have also shown the ability to discriminate between the active and inactive forms of stereoisomers of a drug. This being the case, it should be shown that animals trained to self-administer drugs already considered to be addictive (cocaine, heroin) will determine nicotine to bring about the same effects and without prior training begin self-administering nicotine.

9. Continual ingestion of drugs of addiction results in a tolerance to the dose being consumed. This tolerance results in a constant, spiraling increase in dose to continue to achieve the same desired state of intoxication. It is well documented that smokers develop smoking habits such as to allow them to achieve a relatively constant blood nicotine level. While over the course of years they may even begin to chose products with reduced delivery, they seldom change habits to increase this level.

10. Discontinued use of a drug of addiction results in severe withdrawal symptoms ranging from the mild manifestations of depression, excitation, and severe headaches all the way to the extreme of hallucinations, vomiting, chills, fever, tremors and potentially psychotic behavior.

11. It is our experience (JLC), that individuals that begin smoking start with our full-flavored blended cigarettes and as the smoker ages, switch to lower delivery cigarettes.

12. It is our experience (RAC, JLC, FG→RAC,and others) that smokers continue to smoke for a variety of reasons other than nicotine's purported addictive properties. Our information indicates that nicotine is very important in the sensory response smokers desire during puffing. In addition, other sensory or physical manifestations such as the tactile response to holding a cigarette, the visual response to the smoke, the gustatory response to the cigarettes taste and the association of smoking with pleasurable activities such as drinking coffee or alcoholic beverages, play extremely important roles in the smoking experience.

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